Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/DK05/000140

International filing date: 28 February 2005 (28.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: DK
Number: PA 2004 00313
Filing date: 26 February 2004 (26.02.2004)

Date of receipt at the International Bureau: 11 April 2005 (11.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

PCT/DK 2005/000140

Kongeriget Danmark

Patent application No.: PA 2004 00313

Date of filing: 26 February 2004

Applicant:
(Name and address)

Nordic Bone A/S
c/o Symbion Science Park
Fruebjergvej 3
DK-2100 København Ø
Denmark

Titlel: Strontium-containing compounds for use in prevention or treatment of recrotic bone conditions

IPC: -

This is to certify that the attached documents are exact copies of the above mentioned patent application as originally filed.

Kongeriget Danmark • Patent og Varemærkestyrelsen •

Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

31 March 2005

Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

P10796

Strontium-containing compounds for use in prevention or treatment of necrotic bone conditions

FIELD OF THE INVENTION

The present application relates to compounds and pharmaceutical compositions for use in the treatment and/or prophylaxis of necrotic bone conditions and for methods of treating such conditions.

BACKGROUND OF THE INVENTION

Necrotic bone conditions, such as idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis are severe debilitating conditions. These conditions can be associated with medical interventions such as high dose glucocorticoid therapy and various treatments for HIV/AIDS, or they can arise spontaneously in susceptible individuals or as a consequence of other diseases such as Cushing syndrome, Storage diseases (i.e. Gauchers disease), haemaglobinopathies (e. g. sickle cell disease), pancreatitis, dysbaric conditions or trauma (e.g. dislocation or fracture).

Osteonecrosis is characterized by distinct histopathological features apparent on radiographs or bone scans performed with or without contrast isotopes. Although diagnostic methods for its identification have improved in recent years with the introduction of new sensitive high resolution MRI and other imaging techniques, no therapeutic agents or medical interventions have been developed to prevent and/or treat this condition.

Several pathological situations can induce osteonecrotic conditions, but among the most common clinical situations are high dose glucocorticoid use and treatments with apoptosis inducing compounds, such as the high dose anti-retroviral treatments administered to HIV infected patients. Glucocorticoids as well as other related steroid hormones are given in high doses to modulate immune-system responses in several clinical situations, such as organ or bone marrow transplant, inflammatory and/or autoimmune diseases and some chronic persistent inflammatory states. As an example it has been estimated that the incidence of avascular necrosis of bone among bone marrow transplant recipients exceeds 8% by 5 years (Socie G et al. *Br J Haematol.* 1994: 86(3): 624-628).

Although most skeletal sites can be affected by osteonecrosis, the condition is most commonly found in the bone of the femoral head underneath the articular surface of the

hip joint. The medical intervention of choice remains orthopedic surgery, where the necrotic bone and affected joint structures are removed and replaced with a suitable implant. In some patients with necrotic bone disease, such as juveniles or patients with severe medical conditions, it can be highly problematic to perform this type of orthopedic surgery, and thus there is an unmet medical need for new medical therapies for prophylaxis and/or treatment of necrotic bone disease.

DESCRIPTION OF THE INVENTION

Accordingly, the present application relates to compounds and pharmaceutical compositions for use in the treatment and/or prophylaxis of necrotic bone conditions and for methods of treating such conditions.

Strontium compositions

Previous studies have shown that various strontium compounds modulate bone loss in osteoporosis. In vitro studies have demonstrated that strontium has a direct stimulatory effect on pre-osteoblastic cell division and maturation, and a direct or matrix-mediated inhibition of osteoclast activity (Reginster, JY, *Curr pharm Des* 2002:8 (21):1907-16). In other words, strontium both works as an anti-resorptive and an anabolic agent. Various salts of strontium are known from the prior art, such as, e.g., strontium lactate, strontium chloride and strontium ranelate (distrontium salt of 2-[N,N-di(carboxymethyl)amino]-3-cyano-4-carboxymethylthiophene-5-carboxylic acid) described in EP-B 0 415 850. The ranelate part of the strontium compound, derived from ranelic acid, is unlikely to have any therapeutic effect towards cartilage or bone conditions per se. Other known strontium salts are e.g., strontium tartrate, strontium lactate, strontium phosphate, strontium carbonate, strontium nitrate and strontium sulfate.

Bone consists of an organic matrix comprising predominantly collagen type I, and an inorganic phase comprising calcium phosphate and calcium carbonate. The central portion of collagen is arranged in a triple helical structure containing a regular amino acid sequence with nearly every third residue being glycine. Collagen type I constitutes 85 – 90 % of the organic bone matrix, with remainder being made up of proteins such as bone sialo protein (BSP), osteocalcin and osteonectin. All these proteins are synthesized by the osteoblast, which is the sole cell type responsible for synthesis of the bone matrix. Formation of the organic bone matrix in turn serves as a scaffold for precipitation of the inorganic calcium salts of the bone mineral matrix, and gives the bone its structural strength. Degradation of bone is almost exclusively mediated by the multinuclear osteoclasts, which secretes acids responsible for dissolving the inorganic bone matrix and

enzymes responsible for degrading the proteins of the organic bone matrix.

Normally the processes of bone resorption and bone formation are tightly coupled. Thus when bone resorption is reduced e.g. by an anti-resorptive agent, such as a bisphosphonate, bone formation will also be reduced to an almost similar extent. Conversely, if bone formation is increased e.g. by an anabolic treatment such as the hormone PTH, osteoclast recruitment and activity will also be up regulated. The unique properties of strontium compounds are related to the ability of the strontium ion to uncouple bone formation and resorption processes, thus resulting in a sustained net positive bone balance. This is due to the combined actions of the strontium ion to reduce bone resorption and to increase or stabilize bone formation. In addition to this beneficial effect, we have surprisingly found that the strontium ion has an anti-apoptotic effect on bone cells, which can protect them from conditions inducing apoptosis such as high dose glucocorticoid treatment or systemic administration of pro-apoptotic drugs such as some forms of anti-retroviral or anti-neoplastic treatment. This finding is of therapeutic interest for the prevention and treatment of necrotic bone conditions, which in fact appear to be associated with apoptosis of osteocytes and/or osteoblasts. Such strontium compounds could also include, but is not limited to, strontium ranelate, strontium glutamate, strontium lactate, strontium aspartate or any other organic or inorganic strontium salt. These surprising effects of strontium form the rationale for the use of strontium containing compounds for the prevention and/or treatment of osteonecrotic bone conditions as disclosed in this invention.

Thus, the invention relates to a pharmaceutical composition comprising a therapeutic and/or prophylactic effective amount of one or more components containing a strontium compound together with one or more physiologically acceptable excipients.

According to our discovery, the strontium compound may be administered alone or in combination with other pharmaceutical compounds.

The following strontium salts of organic or inorganic acids may be in a composition as described above. The salts may be in hydrate, anhydrous, solvate, polymorphous, amorphous, crystalline, microcrystalline or polymeric form. In one embodiment of the invention only non-radioactive isotopes of strontium are used.

The inorganic acid for making strontium salts may be selected from the group consisting of boric acid, bromous acid, carbonic acid, chloric acid, diphosphoric acid, disulfuric acid,

dithionic acid, dithionous acid, fulminic acid, hydrazoic acid, hydrobromic acid, hydrochloric acid, hydrofluoric acid, hydroiodic acid, hydrogen sulfide, hypophosphoric acid, hypophosphorous acid, iodic acid, iodous acid, metaboric acid, metaphosphoric acid, metaphosphorous acid, metasilicic acid, nitric acid, nitrous acid, orthophosphoric acid, orthophosphorous acid, orthosilicic acid, phosphoric acid, phosphinic acid, phosphonic acid, phosphorous acid, pyrophosphorous acid, selenic acid, sulfonic acid, sulfuric acid, sulfurous acid, thiocyanic acid and thiosulfuric acid.

The organic acid may be selected from the group consisting of acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_4(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, malonic acid, lactic acid, citric acid, tartaric acid, oxalic acid, ascorbic acid, benzoic acid, salicylic acid, pyruvic acid, L- and D-aspartic acid, phthalic acid, carbonic acid, formic acid, methanesulfonic acid, ethanesulfonic acid, camphoric acid, gluconic acid, L- and D-glutamic acid, trifluoroacetic acid, ranelic acid, 2,3,5,6-tetrabromobenzoic acid, 2,3,5,6-tetrachlorobenzoic acid, 2,3,6-tribromobenzoic acid, 2,3,6-trichlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4-dihydroxybenzoic acid, 2,6-dinitrobenzoic acid, 3,4-dimethoxybenzoic acid, abietic acid, acetoacetic acid, acetonedicarboxylic acid, aconitic acid, acrylic acid, adipic acid, alanine, alpha-ketoglutaric acid, anthranilic acid, benzilic acid, arachidic acid, arginine, aspartic acid, asparagine, azelaic acid, behenic acid, benzenesulfonic acid, beta-hydroxybutyric acid, brassidic acid, capric acid, chloroacrylic acid, cinnamic acid, citraconic acid, crotonic acid, cyclopentane-1,2-dicarboxylic acid, cyclopentanecarboxylic acid, cystathionine, ranelic acid, decanoic acid, erucic acid, ethylenediaminetetraacetic acid, fulvic acid, fumaric acid, gallic acid, glutaconic acid, glutamic acid, glutamine, glutaric acid, gulonic acid, glycine, heptanoic acid, hexanoic acid, histidine, humic acid, hydroxystearic acid, isoleucine, isophthalic acid, itaconic acid, lanthionine, lauric acid (dodecanoic acid), leucine, levulinic acid, linoleic acid (cis,cis-9,12-octadecadienoic acid), lysine, malic acid, m-chlorobenzoic acid, melissic acid, mesaconic acid, methacrylic acid, monochloroacetic acid, myristic acid, (tetradecanoic acid), nonanoic acid, norvaline, octanoic acid, oleic acid (cis-9-octadecenoic acid), ornithine, oxaloacetic acid, palmitic acid (hexadecanoic acid), p-aminobenzoic acid, p-chlorobenzoic acid, petroselic acid, phenylacetic acid, phenylalanine, p-hydroxybenzoic acid, pimelic acid, propiolic acid, propionic acid, proline, serine, p-tert-butylbenzoic acid, p-toluenesulfonic acid, threonine, tryptophan, tyrosine, pyruvic acid, sarcosine, sebacic acid, serine, sorbic acid, stearic acid (octadecanoic acid), suberic acid, succinic acid, terephthalic acid, tetrolic acid, threonine, thyronine, tricarballylic acid, trichloroacetic acid, trimellitic acid, trimesic acid, tyrosine, ulmic acid, valine and cylohexanecarboxylic acid.

All acids, which the United States Food and Drug Administration (FDA) has regarded as safe for use in compositions for oral intake, may be used in the present invention. Examples of suitable acids are mentioned in the following table I:

5

Table I: Acids for making strontium salts

ACETIC ACID,
N-ACETYL-L-METHIONINE
ACONITIC ACID
ACRYLIC ACID-2-ACRYLAMIDO-2-METHYL PROPANE SULFONIC ACID COPOLYMER
ADIPIC ACID
ALGINIC ACID
P-AMINOBENZOIC ACID
ANISIC ACID
ASCORBIC ACID
L-ASPARTIC ACID
D-ASPARTIC ACID
BENZOIC ACID
BORIC ACID
BUTTER ACIDS
BUTYRIC ACID
CHOLIC ACID
CINNAMIC ACID
CITRIC ACID
CYCLOHEXANEACETIC ACID
CYCLOHEXANECARBOXYLIC ACID
DECANOIC ACID
4-DECENOIC ACID
5-DECENOIC ACID
6-DECENOIC ACID
9-DECENOIC ACID
DEHYDROACETIC ACID

DESOXYCHOLIC ACID
2,4-DIHYDROXYBENZOIC ACID
3,7-DIMETHYL-6-OCTENOIC ACID
2,4-DIMETHYL-2-PENTENOIC ACID
(E)-2-DECENOIC ACID
EDTA, CALCIUM DISODIUM
(E)-2-HEPTENOIC ACID
(E)-2-NONENOIC ACID
(E)-2-OCTENOIC ACID
ERYTHORBIC ACID
ETHANESULFONIC ACID, 2-(1-(DIFLUORO-((TRIFLUOROETHENYL)O
2-ETHYLBUTYRIC ACID
4-ETHYLOCTANOIC ACID
FATTY ACIDS
FOLIC ACID
FORMIC ACID
FUMARIC ACID
D-GLUCONIC ACID
L-GLUTAMIC ACID
D-GLUTAMIC ACID
GLYCOCHOLIC ACID
HEPTANOIC ACID
HEXANOIC ACID
TRANS-2-HEXENOIC ACID
3-HEXENOIC ACID
HYDROCHLORIC ACID
4-HYDROXYBENZOIC ACID
1-HYDROXYETHYLIDENE-1,1-DIPHOSPHONIC ACID
3-HYDROXY-2-OXOPROPIONIC ACID
ISOBUTYRIC ACID
ISOVALERIC ACID

ALPHA-KETOBUTYRIC ACID
LACTIC ACID
LAURIC ACID
LEVULINIC ACID
LIGNOSULFONIC ACID
LINOLEIC ACID
L-MALIC ACID
MALIC ACID
2-MERCAPTOPROPIONIC ACID
METHACRYLIC ACID-DIVINYLBENZENE COPOLYMER
2-METHOXYBENZOIC ACID
3-METHOXYBENZOIC ACID
4-METHOXYBENZOIC ACID
TRANS-2-METHYL-2-BUTENOIC ACID
2-METHYLBUTYRIC ACID
3-METHYLCROTONIC ACID
2-METHYLHEPTANOIC ACID
2-METHYLHEXANOIC ACID
5-METHYLHEXANOIC ACID
4-METHYLNONANOIC ACID
4-METHYLOCTANOIC ACID
3-METHYL-2-OXOBUTANOIC ACID
3-METHYL-2-OXOPENTANOIC ACID
4-METHYL-2-OXOPENTANOIC ACID
3-METHYLPENTANOIC ACID
4-METHYLPENTANOIC ACID
2-METHYL-2-PENTENOIC ACID
2-METHYL-3-PENTENOIC ACID
2-METHYL-4-PENTENOIC ACID
4-(METHYLTHIO)-2-OXOBUTANOIC ACID
2-METHYLVALERIC ACID
MONOCHLOROACETIC ACID--PROHIBITED

MYRISTIC ACID
NONANOIC ACID
NORDIHYDROGUAIARETIC ACID--PROHIBITED
9,12-OCTADECADIENOIC ACID (48%) AND 9,12,15-OCTADECATRIENOIC ACID
OCTANOIC ACID
OLEIC ACID
OLEIC ACID, FROM TALL OIL FATTY ACIDS
2-OXOPENTANEDIOIC ACID
2-OXO-3-PHENYLPROPIONIC ACID
PALMITIC ACID
4-PENTENOIC ACID
PERACETIC ACID
PERIODIC ACID
PHENOXYACETIC ACID
PHENYLACETIC ACID
3-PHENYLPROPIONIC ACID
PHOSPHORIC ACID
POLYMALEIC ACID
PROPIONIC ACID
PYROLIGNEOUS ACID
PYROLIGNEOUS ACID, EXTRACT
PYRUVIC ACID
SALICYLIC ACID
SORBIC ACID
STEARIC ACID
SUCCINIC ACID
SULFURIC ACID
SULFUROUS ACID
TANNIC ACID
TARTARIC ACID, L
TAUROCHOLIC ACID

1,2,5,6-TETRAHYDROCUMINIC ACID
THIODIPROPIONIC ACID
TRIFLUOROMETHANE SULFONIC ACID
UNDECANOIC ACID
10-UNDECENOIC ACID
N-UNDECYLBENZENESULFONIC ACID
VALERIC ACID
VANILLIC ACID

In one embodiment of the invention the acid may be a monoprotic or a diprotic acid. In yet another embodiment of the invention, the acid may be an amino acid in either the L-form or D-form.

The strontium salt for use according to the invention may be water soluble, having a water solubility of at least 1 g/l, such as, e.g., at least 5 g/l, at least 10 g/l, at least 20 g/l, at least 30 g/l, at least 40 g/l, at least 50 g/l, at least 60 g/l, at least 70 g/l, at least 80 g/l, at least 90 g/l or at least 100 g/l measured at temperature of 25°C.

Specific examples of strontium salts for use according to the invention are strontium chloride, strontium chloride hexahydrate, strontium citrate, strontium malonate, strontium succinate, strontium fumarate, strontium ascorbate, strontium aspartate in either L and/or D-form, strontium glutamate in either L- and/or D-form, strontium alpha-ketoglutarate strontium pyruvate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate, strontium ranelate and mixtures thereof.

Other examples of relevant acids for making strontium salts for use in a pharmaceutical composition may be found in WO 00/01692, which is hereby incorporated by reference.

In a preferred embodiment of the invention, the strontium salt is composed of a strontium ion complexed to a di-carboxylic organic acid. Such a salt may also be a salt of an amine or an amino acid or mixtures thereof. A strontium salt of a di-carboxylic acid may be selected so the di-carboxylic acid moiety of the composition has a higher dissolution constant to strontium ions compared to calcium ions under physiological conditions. Thus, the dissolved salt will provide a solution with preferential binding of free calcium ions which may provide an advantage for promoting intestinal absorption of the strontium ion

and thus improving the therapeutic effect and/or reducing the required dose necessary to achieve the prophylactic and/or therapeutic effect in the osteonecrotic condition.

As exemplified by the salts mentioned above, the counter ions in the strontium compounds may be active substances having the similar physiologic effects on bone metabolism as the present inventors previously found for strontium. Examples of such compounds are e.g., strontium glutamate, strontium aspartate, strontium bisphosphonate salts, calcium glutamate and calcium alpha-ketoglutarate.

In certain cases it may be beneficial to further add one or more active substances to a pharmaceutical composition according to the invention. The one or more active substances may have a therapeutic and/or prophylactic effect on a bone disease and/or other conditions such as osteonecrosis. The term "active substance having a therapeutic and/or prophylactic effect on diseases and conditions affecting metabolism and structural integrity of bone" includes active substances that can attain a particular medical result, such as, e.g., reduce the incidence of osteonecrosis, increase bone density and/or improve healing of bone or prevent the occurrence of fracture in a subject at risk of developing an osteonecrotic condition. Examples of such substances are bone anti-resorptive and/or anabolic agents. However, one or more active substances having other effects than those mentioned above may also be included in a pharmaceutical composition of the invention. Such active substances could be e.g. pain relievers (analgesic agents), anti-inflammatory agents, anti-retroviral agents, anti-neoplastic agents, disease-modifying anti-rheumatic drugs, or other anti-rheumatic drugs.

Specific examples of active substances, which may be used in a pharmaceutical composition according to the invention are calcium-alpha-ketoglutarate, calcium and/or salts thereof, vitamin D such as, e.g., vitamin D3 and/or functional equivalents of vitamin D3, glucagon-like peptide-2, glucagons-like peptide-2 releasing compositions, bisphosphonates, selective estrogen receptor modulators, calcitonin, parathyroid hormone (PTH), parathyroid hormone related peptide, non-steroidal anti inflammatory drugs, tumor necrosis factor alpha (TNF-α) inhibitors, inhibitors of IL-15 release or function, inhibitors of IL-1 release or function, inhibitors of retroviral reverse transcriptase, protease inhibitors used in anti-retroviral treatment, glucosamine sulphate, glutamic acid and/or salts thereof, aspartic acid and/or salts thereof, proline, glutamine and hydroxyproline.

As mentioned above, the compounds and compositions of the present invention may be used for the treatment and/or prophylaxis of various conditions that are associated with

osteonecrotic conditions and/or that are associated with an increased risk of developing an osteonecrotic condition. Thus, the present invention relates to a method for the treatment and/or prophylaxis of an osteonecrotic bone disease and/or conditions, the method comprising administering to a subject in need thereof a therapeutically and/or prophylactically effective amount of a combination of one or more first components containing a strontium compound and one or more second components containing compounds required for treatment or prevention of a disease or condition associated with an increased risk of osteonecrosis. Thus, according to the present invention, a strontium compound may be administered in combination with a glucocorticoid/glucocorticosteroid compound, an anti-retroviral compound and/or another therapeutic substance known to have a pro-apoptotic effect on any cells of the osteoblastic and/or osteoclastic lineage. These administrations may occur simultaneously or separately.

The subject to be treated may be a mammal, such as, e.g. a human or a domestic animal, such as, e.g., a cat, a dog, a horse, a cow or a sheep.

The strontium salt may be administered in a dose corresponding to from about 0.1 to about 17 g daily calculated as anhydrous salt. More specifically, the salt may be administered in a dose corresponding to from about 0.2 to about 15 g daily such as, e.g., from about 0.4 to about 13 g daily, from about 0.6 to about 12 g daily or from about 0.7 to about 11.5 g daily calculated as anhydrous salt.

The daily dose of strontium may be at least about 0.01 g, such as, e.g., at least about 0.025 g, at least about 0.050 g, at least about 0.075 g, at least about 0.1 g, at least about 0.2 g, at least about 0.3 g, at least about 0.4 g or at least about 0.5 g or from about 0.01 g to about 2 g such as, e.g., from about 0.1 g to about 2 g, from about 0.3 g to about 2 g or from about 0.3 g to about 1 g.

The invention also relates to a method wherein the strontium component is administered in the form of a pharmaceutical composition as described above.

The invention further relates to a method wherein the administration may take place one or more times daily, such as from 1 to 5 times daily.

The invention also relates to a method wherein the administration may take place one or more times weekly, such as from 1 to 3 times weekly.

As described above, one or more active substances may be added to a pharmaceutical composition according to the invention, or administered as part of the same treatment as the administration of the strontium compound. Examples of such an active substance are listed below:

Hormones, vitamins and ions known to affect bone metabolism such as

- Vitamin D.
- Activated vitamin D_3 (1,25-dihydroxycholecalciferol)
- Vitamin D_2.
- Alphacalcidol,
- Calcitriol
- Dihydrotachysterol,
- Calcium
- Calcitonin
- Glucagon like peptide 2 (GLP-2)
- PTH
- OsteoProtegrin (OPG)
- Estrogen
- 17β estradiol
- 17α estradiol
- Estriol
- Estrene
- Testosterone

Bisphosphonates such as

- risedronate
- clodronate
- etidronate
- alendronate
- tiludronate
- pamidronate
- zoledronate
- ibandronate

Selective Estrogen Receptor Modulators such as

- Raloxifene
- Levormeloxifene

Basedoxifene
Tamoxifene
Lasofoxifene
Ospemifene
Arzoxifene
Zindoxifene
Tibolone

Pain relieving agents such as
Acetaminophen
Aspirin
Ibuprofen
Naproxen
Ketoprofen
Oxycontin
Flurbiprofen
Indomethacin
Celelcoxib
Valdecoxib
Rofecoxib
Lumiracoxib
Meloxicam

Anti-Rheumatic drugs such as
Methotrexate
Leuflunomide
Cyclosporine
Cyclophosphamide
Azathioprin
Penicillamine
Myocrisin
sulfasalcine

The administration of the strontium compound and any other pharmaceutically active compound may take place simultaneously, either in a single administration form or in separate administration forms for simultaneous administration as described above.

The invention also relates to a kit for use in the treatment and/or prophylaxis of an osteonecrotic bone disease in a mammal, such as, e.g., idiopathic or secondary

osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis osteolytic lesions produced by bone metastasis, bone loss due to sex steroid hormone deficiency, bone abnormalities due to steroid hormone treatment, bone abnormalities caused by cancer therapeutics, osteomalacia, or glucocorticoid-induced osteopenia, the kit comprising at least a first and a second component, the first component comprising a strontium salt and one or more second components comprising at least one of the following: i) a further strontium containing compound, ii) a glucocorticoid containing compound, iii) an anti-retroviral compound, iv) a calcium containing compound, v) a further active substance, such as, e.g. vitamin D, estrogen, a bisphosphonate or a selective estrogen receptor modulator.

Pharmaceutical compositions

The pharmaceutical compositions according to the invention normally comprise the specific compounds together with one or more physiologically acceptable excipients, i.e. a therapeutically inert substance or carrier.

The carrier may take a wide variety of forms depending on the desired dosage form and administration route.

The pharmaceutically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavors, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

Above are mentioned specific examples of the amounts of compounds administered. However, it will be understood that the amount of the compounds actually administered will be determined by a physician in light of the relevant circumstances including the condition to be treated, the choice of compounds to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms and the chosen route of administration. While the present compounds are preferably administered orally, the compounds may also be administered by any other suitable route, such as parenteral administration, administration in a nasal spray, transdermal patches, subcutaneous injection or a suppository.

The pharmaceutical composition comprising a compound according to the invention may be in the form of a solid, semi-solid or fluid composition.

The pharmaceutically acceptable excipients may be e.g. fillers, binders, disintegrants, diluents, glidants, solvents, emulsifying agents, suspending agents, stabilizers, enhancers, flavors, colors, pH adjusting agents, retarding agents, wetting agents, surface active agents, preservatives, antioxidants etc. Details can be found in pharmaceutical handbooks such as, e.g., Remington's Pharmaceutical Science or Pharmaceutical Excipient Handbook.

For parenteral administration a number of formulation methods can be employed as apparent to a person skilled in the art. Such formulations may comprise conventional buffering agents as well as additives such as cyclodextrine, dextrose, maltodextrin, mannitol, povidone or other agents employed in parenteral formulations as disclosed in: Pharmaceutical Dosage Form: Parenteral Medications, Volume 1, 2nd Edition, Chapter 5, p. 194, De Luca and Boylan, "Formulation of Small Volume Parenterals", Table 5: Commonly used additives in Parenteral Products

In one embodiment of the invention, the pharmaceutical composition may be in the form of a tablet. The tablet may be coated with a coating that enables release of at least part of the salt in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum, such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet.

In another embodiment of the invention a compound may be selected have complete or predominant solubility in the ventricle such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet.

The tablet may have a shape that makes it easy and convenient for a patient to swallow. The tablet may thus e.g. have a rounded or a rod-like shape without any sharp edges. Furthermore, the tablet may be designed to be divided in two or more parts.

A semi-solid form of the composition may be a paste, a gel or a hydrogel.

The fluid form of the composition may be a solution, an emulsion including nano-emulsions, a suspension, a dispersion, a liposomal composition, a spray, a mixture, a syrup or an elixir.

Other suitable dosages forms of the pharmaceutical compositions according to the invention may be capsules, sachets, troches, devices etc.

The pharmaceutical compositions may be prepared by any of the methods well known to a person skilled in pharmaceutical formulation.

Specific embodiments of the invention appear from the appended claims.

CLAIMS

1. A method for the treatment and/or prophylaxis of an osteonecrotic bone disease and/or conditions resulting in a dysregulated bone metabolism in a mammal, such as, e.g., a human female or male adult, adolescent or a child, such as, e.g., idiopathic or secondary osteonecrosis, avascular bone necrosis, glucocorticoid induced bone ischemia/osteonecrosis, Legg-Calve-Perthes disease and femoral head necrosis , the method comprising administering to a subject in need thereof a strontium-containing compound (a).

2. A method according to claim 1, wherein the strontium-containing compound (a) is administered in combination with a therapeutic agent known to induce apoptosis and/or necrosis of bone cells (b).

3. A method according to claim 1 or 2, wherein the administration of a strontium compound and an apoptosis and/or necrosis inducing therapeutic agent leads to at least one of the following:

i) reduction in the incidence or severity of osteonecrotic bone disease as defined in claim 1 compared with administration of (b) alone in the same dose, a reduction in incidence being defined as at least 5%, preferably 10%, more preferred 30% or 50% decrease in osteonecrosis in patients treated with a) and b) in combination compared to similar patients treated with b) alone

ii) reduction of frequency and/or magnitude of side-effects of (b) compared with administration of (b) alone in the same doses, side effects being defined as any clinical relevant observation pertaining to the disease or condition in the patient, such as bone-pain, joint-pain, immobility, functional impairment, weight loss or bone mineral density (BMD) decrease

4. A method according to any of claims 1 to 3, wherein the strontium compound is administered in combination with a glucocorticoid and/or another steroid hormone.

5. A method according to claim 1 to 3, wherein the strontium compound is administered in combination with an anti-retroviral compound. such as efavirenz (Sustiva ®), zidovudine (Retrovir®), lamivodine (Epivir®), abacavir (Ziagen®), zalcitabine (Hivid®), didanosine (Videx®), stavudine (Zerit®), tenofovir disoproxil fumarate (Viread®), emtricitabine

(Emtriva®), fosamprenavir (Lexiva®), nevirapine (Viramune®), delavirdine (Rescriptor®), capravirine, enfuvirtide (Fuzeon®), saquinavir (Invirase®, Fortovase®), ritonavir (Norvir®), indinavir (Crixivan®), tipranavir, amdoxovir, elvucitabine, atazanivir (Reyataz®), nelfinavir (Viracept®), amprenavir (Agenerase®), PRO-542, TMC-114, TMC-125, BMS-56190, DPC-0830, .

6. A method according to any of claims 1-5, wherein a) and b) is administered as a single composition.

7. A method according to any of claims 1-5, wherein a) and b) is administered as separate compositions.

8. A method according to any of claims 1-5, wherein the administration of a) and b) take place simultaneously or sequentially.

9. A method according to any of claims 1 to 8, wherein the strontium-containing compound is selected from the group consisting of strontium salts of an organic or an inorganic acid.

10. A method according to claim 9, wherein the inorganic acid is selected from the group consisting of hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, nitrous acid, phosphoric acid, phosphinic acid, phosphonic acid, sulfonic acid, sulfuric acid, sulfurous acid, disulfuric acid and boric acid.

11. A method according to claim 9, wherein the organic acid is selected from the group consisting of acetic acid, C_2H_5COOH, C_3H_7COOH, C_4H_9COOH, $(COOH)_2$, $CH_2(COOH)_2$, $C_2H_4(COOH)_2$, $C_3H_6(COOH)_2$, $C_4H_8(COOH)_2$, $C_5H_{10}(COOH)_2$, fumaric acid, maleic acid, malonic acid, lactic acid, citric acid, tartaric acid, oxalic acid, ascorbic acid, benzoic acid, salicylic acid, phthalic acid, pyruvic acid, L-aspartic acid, D-aspartic acid, carbonic acid, formic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, camphoric acid, gluconic acid, L-glutamic acid, D-glutamic acid, trifluoroacetic acid and ranelic acid.

12. A method according to any of claims 9-11, wherein the acid is a chelator of strontium.

13. A method according to any of claims 9-11, wherein the acid is a non-chelator of strontium.

14. A method according to any of claims 9-11, wherein the acid is an amino acid in either L-form or D-form.

15. A method according to any of claims 9-14, wherein the salt is in hydrate, anhydrous, solvate, polymorphous, amorphous, crystalline, microcrystalline or polymeric form.

16. A method according to any of claims 9-15, wherein the salt is water-soluble.

17. A method according to claim 16, wherein the salt has a water solubility of at least 1 g/l, such as, e.g., at least 5 g/l, at least 10 g/l, at least 20 g/l, at least 30 g/l, at least 40 g/l, at least 50 g/l, at least 60 g/l, at least 70 g/l, at least 80 g/l, at least 90 g/l or at least 100 g/l measured at a temperature of 25°C.

18. A method according to any of claims 9-17, wherein the salt is selected from the group comprising strontium chloride, strontium carbonate, strontium citrate, strontium malonate, strontium succinate, strontium fumarate, strontium ascorbate, strontium pyruvate, strontium L-glutamate, strontium D-glutamate, strontium L-aspartate, strontium D-aspartate, strontium alpha-ketoglutarate, strontium lactate, strontium tartrate, strontium glutarate, strontium maleate, strontium methanesulfonate, strontium benzenesulfonate, strontium ranelate and mixtures thereof.

19. A method according to any of claims 9-18, wherein the acid is a monoprotic or a diprotic acid.

20. A method according to any of claims 9-19, wherein the strontium salt is in a hydrated form such as a mono-hydrate, di-hydrate, tetra-hydrate, penta-hydrate, hexa-hydrate, hepta-hydrate, octa-hydrate, nona-hydrate or decahydrate.

21. A method according to claim 1-20, wherein the daily dose of strontium is at least about 0.01 g, such as, e.g. at least about 0.025 g, at least about 0.050 g, at least about 0.075 g, at least about 0.1 g, at least about 0.2 g, at least about 0.3 g, at least about 0.4 g or at least about 0.5 g or from about 0.01 to about 2 g such as, e.g., from about 0.1 to about 2 g, from about 0.1 to about 1 g, from about 0.15 to about 0.5 g, from about 0.3 to about 2 g or from about 1 to about 2 g.

22. A method according to any of claims 1-21, the method comprising administering an amount of strontium and an amount of bisphosphonate to a subject in need thereof.

23. Use of a strontium-containing compound alone or in combination with another therapeutic agent where the strontium containing compound is used to prevent and/or treat an osteonecrotic bone condition as defined in claim 1, and where the medical treatment comprise identification and/or monitoring the patients in need of treatment by imaging techniques such as X-ray, ultrasound, magnetic resonance imaging of the skeletal site suspected to be at risk for osteonecrosis and/or by assessment of altered bone turnover by the use of specific biochemical markers of bone turnover.

24. Use of a) a strontium-containing compound together with b) one or more further active substances capable of reducing the incidence of bone necrosis and/or reduce apoptosis of bone cells such as osteoclasts and osteoblasts as well as their precursors according to any of claims 1-23, for the manufacture of a medicament comprising a concentration of a) and b) that is effective in preventing and/or treating a necrotic bone condition.

25. A pharmaceutical composition comprising a) a strontium-containing compound alone or in combination with b) one or more further active substances used in the medical management of patients suffering from a condition known to be associated with elevated risk for incidence or progression of a necrotic bone condition according to any of claims 1-24, together with one or more physiologically acceptable excipients.

26. A pharmaceutical composition according to claim 25 in the form of a tablet.

27. A pharmaceutical composition according to claim 26, wherein the tablet is coated with a coating that enables release of at least part of the salt in the proximal part of the small intestine, such as e.g. the duodenum and/or the proximal jejunum such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet.

28. A pharmaceutical composition according to claim 26, wherein the tablet have complete or predominant solubility in the ventricle such as at least 50% w/w, at least 60% w/w, at least 65% w/w, at least 70% w/w, at least 80% w/w or at least 90% w/w of the total amount of the salt contained in the tablet

29. A pharmaceutical composition according to claim 25 formulated for parenteral administration to a patient in need thereof.

30. A pharmaceutical composition according to claim 26-28, wherein the tablet has a shape that makes it easy and convenient for a patient to swallow.

31. A pharmaceutical composition according to claim 30, wherein the tablet has a rounded or a rod-like shape without any sharp edges.